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(54) PROCESSES AND COMPOSITIONS FOR REMINERALIZATION OF DENTAL ENAMEL

(71) We, THE PROCTER & GAMBLE COMPANY, a corporation organised and existing under the laws of the State of Ohio, United States of America, of 301 East Sixth Street, Cincinnati, Ohio 45202, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to processes and compositions which are useful to remineralize subsurface dental enamel. More specifically, this invention relates to salt solutions, such as calcium and phosphate salt solutions, which are sequentially applied to dental enamel resulting in remineralization of subsurface dental enamel.

It is well known in the dental art that dental caries begins as a subsurface demineralization ("white spot") of the dental enamel and that remineralization may be of importance in retarding or arresting dental caries. U.S. Patent 3,679,360, July 25, 1972, to Rubin et al., discloses a method, the purpose of which is to deposit calcium phosphate from a gel medium onto the surface of a tooth. But this method of remineralizing has several disadvantages. Remineralization occurs only on the surface of the tooth whereas the initial cause of dental caries is subsurface demineralization. The surface on which apatite growth is desired must be prepared (as by roughening), and the tooth and coatings must be covered by a suitable cap for several days while the mineralization of the tooth surface occurs.

The disadvantages of the method disclosed in the Rubin et al. patent are overcome by the present invention which provides for subsurface remineralization rather than surface remineralization. Since dental caries begins as a subsurface demineralization of the dental enamel, subsurface remineralization arrests and repairs the carious lesion before any permanent structural damage to the tooth occurs. The present invention does

not require preparation of the enamel surface, capping of the tooth, or removal of decay products. Further, the present invention may be conveniently practiced by the public without substantially changing their dental care habits.

The present invention provides an oral treatment pack comprising as components adapted for sequential application (in either order) to dental tissue:—

- (A) a first component which comprises a cation in water-soluble form, which cation is capable of forming an insoluble precipitate; and
- (B) a second component which comprises an anion in water-soluble form, which anion is capable of forming with said cation an insoluble precipitate adapted to remineralize subsurface dental enamel,

wherein one or both of the components contains a flavouring agents, the components being compatible with the oral environment and being such as to have a pH from 3 to 10 solution.

Concentrations of cationic and anionic solutions for use as the components of the invention may generally be from 0.005% to 10% (or the limit of solubility of the salt), with from 0.05% to 5% being preferred. (These percentages are by weight). More than one cation may be employed in the cationic solution. Similarly, more than one anion may be employed in the anionic solution.

The application of the oral treatment pack of the invention involves:

- (1) applying one of the components to the surface of a tooth having a demineralized subsurface for a period of time sufficient to allow the said ion of that component to diffuse into the demineralized subsurface, and thereafter
- (2) applying the other component to the

surface of the tooth whereby the said ion of that other component is diffused into the demineralized subsurface and the said insoluble precipitate is thereby formed.

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The remineralizing precipitate formed is less susceptible to demineralization than original enamel if heavy metal cations and fluoride anions are employed.

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There is a visible effect on "white spots" after as few as eight sequential applications, and it is contemplated that several sequential applications will be employed to achieve the most beneficial results.

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The present invention involves the discovery that subsurface dental enamel may be remineralized by the sequential application of certain soluble salts yielding ions which will react to form a remineralizing precipitate. The sequential application consists of two steps which may be performed in either order, although the following order is slightly preferred. In the first step, one component is placed in contact with the tooth surface nearest to the demineralized subsurface. This, first component preferably contains the stated cations, and they diffuse through the tooth surface to its demineralized subsurface.

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In the second step, the other component containing the stated anions is placed in contact with the tooth surface nearest the demineralized subsurface. The anions diffuse through the tooth surface to the demineralized subsurface where they come in contact with the cations previously deposited and form a precipitate which is bound to the tooth structure. As a result, the tooth's subsurface is remineralized.

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Concentrations of the salt solutions are generally from 0.005% to 10% or the limit of solubility of the salt, as stated above. Excess salt can be present, if desired. Concentrations from about 0.05% to about 5% are preferred. The concentrations of the soluble salts containing the desired anions are essentially the same as those for the water-soluble salts containing the desired cations. Equivalent concentrations are not necessary since in each step an excess of the reactant is desirable in order to promote diffusion into the tooth's demineralized subsurface.

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While the length of time of contact between the salt solutions and the tooth's surface is not critical, it is necessary for the length of time to be great enough to allow diffusion of the ions through the tooth's surface to the demineralized subsurface. It is believed that at least ten seconds is required for this diffusion.

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Each solution should have a pH of from 3 to 10 before and after the precipitation reaction, and be otherwise compatible in the oral environment. The ions must not combine

prematurely in the pack to form a precipitate, but ions from each component must be able to diffuse through the surface of the tooth to a demineralized subsurface area and be able to form an insoluble salt with ions of the other component.

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The solutions and the insoluble precipitates are preferably not colored, and, of course, must have acceptable levels of toxicity.

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Although many precipitates are within the broad scope of this invention, by depositing a precipitate less soluble than the original enamel, the remineralized subsurface can be made to be more resistant to demineralization than was the original enamel. If the remineralization contemplated by this invention is carried out in the presence of either a heavy metal ion or fluoride ion, the remineralized enamel is more resistant to demineralization than was the original enamel. If both ions are present, the remineralized enamel is even more resistant to demineralization. The concentration of salt containing heavy metal ion and fluoride ion in their respective solutions may be from 0.005% to 10%, in accordance with the limits given above, but from 0.005% to 0.1% is preferred.

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Examples of suitable heavy metal ions are barium, lanthanum, manganese, lead, tin, zinc, indium, zirconium, iron, titanium, vanadium, and cadmium. Indium is preferred.

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In the most preferred embodiment of the present invention, the remineralizing cationic solution contains from about 0.005% to about 10%, preferably about 1%, of a soluble calcium salt yielding calcium ions and from about 0.005% to about 10%, preferably from about 0.005% to 0.1% of a soluble indium salt yielding indium ions. The remineralizing anionic solution contains from about 0.005% to about 10%, preferably about 1%, of soluble phosphate salt yielding phosphate ions and from about 0.005% to about 10%, preferably from about 0.005% to about 0.1% of a soluble fluoride salt yielding fluoride ions.

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The resulting precipitate is a calcium phosphate or hydroxylapatite, the natural constituent of tooth enamel, with incorporated indium and fluoride ions. Not only does this process result in remineralized enamel, but the remineralized enamel is more resistant to subsequent demineralization than was the original enamel.

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Soluble fluoride and indium salts which are suitable for use in solutions of the present invention include, but are not limited to, sodium fluoride, zinc fluoride, betaine fluoride, alanine stannous fluoride, hexylamine fluoride, indium chloride, indium sulfate, and indium nitrate. Suitable salts for other desired cations and anions would be obvious to one skilled in the art.

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The anions which give desirable insoluble precipitates include phosphate, C_8-C_{18} fatty acyl groups, fluoride, fluorophosphate, silica fluoride, molybdate, sulfate, tungstate, β -hydroxyquinolate, tartrate, sorbate, C_6-C_{18} alkyl sulfonates, carbonates, iodates, etc. Mixtures of these anions are desirable.

Cations which give desirable insoluble precipitates are calcium, zinc, indium, rare earth metals, magnesium, manganese, cadmium, aluminum, barium, lanthanum, zirconium, strontium, cesium, etc. Mixtures of these cations are desirable.

These cations and anions which form the insoluble remineralizing precipitates are obtained from solutions of the corresponding soluble salts. Suitable soluble salts of the cations used in this invention include the chloride, acetate and gluconate salts of the desired cation. Similarly suitable soluble salts of the anions of this invention include sodium, potassium, ammonium, and substituted ammonium salts.

The many different cations and anions with which one could remineralize tooth enamel combine to form many different precipitates. Most preferred precipitates are calcium phosphate compounds with small amounts of indium and fluoride incorporated therein. The following precipitates disclose not only desirable remineralizing precipitates but, of course, also the cations and anions necessary to form the precipitates. It will be recognized by one skilled in the art that some of these precipitates can be formed by first forming an original precipitate which then further reacts to form the indicated precipitate. For example, a hydroxide may form first and then react further to form the corresponding oxide.

Preferred precipitates are: $CaMoO_4$; $CaWO_4$; $ZnNH_4PO_4$; $InPO_4$; rare earth phosphates such as lanthanum, cerium, and samarium (II) phosphate; rare earth fluorides such as lanthanum, cerium, praseodymium, neodymium, and samarium fluorides; magnesium alkyl (C_{18}) sulfonate; magnesium stearate; calcium stearate; cadmium iodate, cadmium hydroxide; Ca phosphates, Zn stearate; Al phosphates.

As discussed before, the cations of the above precipitates are readily obtained from a solution of the corresponding soluble salts, e.g., the chloride salts. The anions of the above precipitates are readily obtained from solutions of the corresponding soluble salts, e.g., sodium, potassium or ammonium salts.

Other precipitates contemplated by this invention are: Aluminum oxide; aluminum hydroxide; barium soaps; Ba stearate; Ba palmitate; Ba myristate; Ba laurate; barium fluorophosphate; barium silicofluoride; barium molybdate; barium phosphates $Ba_3(PO_4)_2$, $BaHPO_4$, and $Ba(H_2PO_4)_2$ mixed; barium sulfate; barium tungstate; indium 8 -

hydroxyquinolate; indium hydroxide; indium phosphate; lanthanum tartrate; lanthanum sorbate; lanthanum oxalate; lanthanum oxide; lanthanum tungstate; lanthanum phosphate; magnesium 8 - hydroxyquinolate (oxine); magnesium alkyl sulfonates such as magnesium n - decyl sulfonate, magnesium lauryl sulfonate, magnesium myristyl sulfonate, magnesium cetyl sulfonate, and magnesium n - octadecyl sulfonate; magnesium oleate; magnesium myristate; magnesium palmitate; magnesium stearate; magnesium laurate; magnesium carbonate; magnesium fluoride; magnesium phosphates; magnesium ammonium phosphate; manganese carbonate; manganese hydroxide; manganese ammonium phosphate; nickel hydroxide; laurate; myristate; palmitate; stearate; lead phosphate (ortho); stannous oxalate; zinc tartrate; zinc hydroxyquinolate; zinc carbonate; zinc oxalate; zinc hydroxide; zinc phosphate (usually complex mixtures); zinc ammonium phosphate; zirconium hydroxide; zirconium phosphate; calcium carbonate; calcium molybdate; calcium silicate; calcium tungstate; calcium lauryl sulfonate; calcium myristyl sulfonate; calcium n - hexadecyl sulfonate; calcium n - octadecyl sulfonate; calcium oleate; calcium stearate; calcium tartrate; calcium aluminates; calcium hydroxide; calcium ammonium phosphate; tricalcium phosphate; dicalcium phosphate; calcium monofluorophosphate; Li_3PO_4 ; $MgHPO_4$; $Mg_3(PO_4)_2$; $MgNH_4PO_4$; aluminium phosphates; aluminium orthophosphate; calcium phosphates; zinc phosphates; strontium phosphate; indium; tin; barium phosphate; ceric phosphate;

$Al(OH)_3$; $In(OH)_3$; $Mg(OH)_2$; MoO_3 ;

SiO_2 ; $SiO_2 \cdot xH_2O$; $Sn(OH)_2$; $SnO \cdot xH_2O$;

$Ti(OH)_4TiO_2$; V_2O_5 ; WO_3 ; and $Zn(OH)_2$.

Since the cationic and anionic components of the remineralization precipitate must be delivered to the tooth surface in a sequential manner, it is necessary to employ a delivery system which meets this requirement. The oral treatment pack can comprise two separate delivery vehicles, each containing one component. Or the oral treatment pack can consist of one vehicle which contains both components segregated so as to be released in a sequential manner.

Examples of two vehicle systems, in which cationic components are in one vehicle and anionic components are in another vehicle are: Mouthwash-mouthwash; toothpaste-toothpaste; toothpaste-mouthwash; mouth-

wash-toothpaste; beverage-beverage; candy drop-candy drop; nutritional substance-nutritional substance; toothpowder-toothpowder; and so forth.

- 5 Examples of one vehicle systems where some means is provided for sequential release of the components include, but are not limited to, a metastable system in which ions are released at different times; a toothpaste in which one ingredient is encapsulated for delayed release; a two-compartment bottle; a lozenge with a laminated structure so that first one ionic ingredient is released and then another; a chewing gum made so that one ingredient is released before the other; a nutritional substance in which one ingredient is released before the other; and so forth.

- 20 The flavouring agents may of course be any of those conventionally used in oral compositions (e.g. toothpastes, chewing gums, lozenges). In addition the oral treatment pack may contain other useful ingredients such as compatible therapeutic agents, sudsing agents, sweeteners, coloring agents, abrasives, thickeners, preservatives, and stabilizers. Examples of such ingredients are disclosed in U.S. Patent 3,175,951, Tucker et al., March 30, 1965.

- 30 The two components of several oral treatment packs which are embodiments of this invention are set forth in the following examples which are given to further illustrate the present invention.

EXAMPLE I Cationic Mouthwash

Ingredient	% by weight
Indium trichloride (2.89% solution in H ₂ O)	1.000
Calcium trichloride	1.109
40 Glycerin, U.S.P.	10.000
Ethanol, 190-proof, U.S.P.	7.500
Flavor	0.170
Polyoxyethylene (20) sorbitan monoisostearate	0.450
45 Sodium saccharin, N.F.	0.090
Boric acid, U.S.P.	0.075
Glacial acetic acid, A.C.S.	0.200
NaOH (10% solution in H ₂ O)	0.400
50 FD&C Yellow #5 (1% solution)	0.140
Distilled water	78.866
	100.000

Anionic Mouth Rinse

Ingredient	% by weight	
Sodium fluoride	0.033	55
Disodium phosphate	0.847	
Glycerin, U.S.P.	10.000	
Ethanol, 190-proof, U.S.P.	7.500	
Flavor	0.040	
Polyoxyethylene (20) sorbitan monoisostearate	0.200	60
Sodium saccharin, N.F.	0.050	
Boric acid, U.S.P.	0.075	
FD&C Green (1% solution)	0.045	
Distilled water	81.210	65
	100.000	

EXAMPLE II Anionic Dentifrice

Ingredient	% by weight	
Disodium phosphate	3.820	70
Sodium fluoride	0.200	
Abrasive (precipitated silica gel)	19.000	
Sorbitol (30% in water)	25.000	
Glycerin	11.000	75
Hydroxyethylcellulose	1.500	
Keltrol (a polysaccharide)	0.650	
Sodium alkyl sulfate (28% in water)	3.500	
Saccharin	0.250	80
Titanium dioxide	0.500	
Flavor	0.900	
Color	0.350	
Concentrated hydrochloric acid	2.336	85
Water	balance	

Cationic Dentifrice

Ingredient	% by weight	
Calcium chloride	5.000	
Indium trichloride (2.89% solution in H ₂ O)	6.000	90
Abrasive (precipitated melamine formaldehyde condensation product)	37.000	
Sorbitol (30% in water)	24.500	95
Glycerin	5.700	
Hydroxyethylcellulose	1.300	
Keltrol (a polysaccharide) (Registered Trade Mark)	0.600	
Sodium alkyl sulfate (28% in H ₂ O)	4.200	100
Saccharin	0.220	
Flavor	0.970	
Color	0.500	
Water	balance	105
Hydrochloric acid to pH 3.5		

EXAMPLE III
Multilayered Lozenge
Cationic Portion

Ingredient	% by weight
5 Sorbitol	17.5
Mannitol	17.5
Starch	13.6
CaCl ₂ · 2H ₂ O	4.7
InCl ₃	0.04
10 Sugar substitute (Niehaus)	1.2
Flavor	11.7
Color	0.1
Corn syrup	balance

Anionic Portion

Ingredient	% by weight
15 Sorbitol	17.6
Mannitol	17.6
Starch	13.7
Na ₂ HPO ₄	3.9
20 NaF	0.4
Sugar substitute (Niehaus)	1.2
Flavor	12.7
Color	0.1
Corn syrup	balance

EXAMPLE IV
Toothpowder
Cationic Portion

Ingredient	% by weight
30 Sodium alkyl sulfate	1.00
Indium trichloride	0.0289
Sodium citrate	1.50
Flavor	1.50
Saccharin	0.29
Abrasive	balance

Anionic Portion

Ingredient	% by weight
35 Sodium alkyl sulfate	1.00
Disodium phosphate	3.82
Sodium fluoride	0.20
40 Sodium citrate	1.50
Flavor	1.50
Saccharin	0.29
Abrasive	balance

EXAMPLE V
Chewing Gum
Cationic Portion

Ingredient	% by weight
Gum base	
50 30 parts Estergum	
45 parts Coumarone resin	
15 parts dry Latex	
10 parts Paraffin wax	
(M.P.=180°F.)	30.00
Sugar	50.00
55 Corn syrup	18.00
InCl ₃	0.0289
CaCl ₂	5.00
Citric acid	1.00
Flavor	balance

Ingredient	Anionic Portion	% by weight
Gum base		
30 parts Estergum		
45 parts Coumarone resin		
15 parts dry Latex		
10 parts Paraffin wax		
(M.P.=180°F.)		30.00
Sugar		50.00
Corn syrup		18.00
Na ₂ HPO ₄		3.82
NaF		0.20
Citric acid		1.00
Flavor		balance

Combinations of any of the above anionic with any of the above cationic compositions can also be used. When the above compositions are used in sequence in the human mouth in their normal amounts, demineralized subsurfaces of teeth are remineralized and the resulting tooth structures are less susceptible to re-demineralizations. The concentration of the combination of the calcium and indium salts and the combinations of the phosphate and fluoride salts in the human mouth in use are respectively about 2% and about 1%.

As an Example of the use of the oral treatment packs of the Examples a subject rinses his mouth with the cationic mouthwash of Example I and then rinses his mouth with the anionic mouthwash of Example I. Each rinse is performed for about 30 seconds. The cationic-anionic sequence is performed twice a day for four days.

WHAT WE CLAIM IS:—

1. An oral treatment pack comprising as components adapted for sequential application (in either order) to dental tissue:

(A) a first component which comprises a cation in water-soluble form, which cation is capable of forming an insoluble precipitate; and

(B) a second component which comprises an anion in watersoluble form, which anion is capable of forming with said cation an insoluble precipitate adapted to remineralize subsurface dental enamel,

wherein one or both of the components contains a flavouring agent, the components being compatible with the oral environment and being such as to have a pH from 3 to 10 in solution.

2. A pack as recited in claim 1 wherein the said cation and anion are present in their respective components in the form of compounds which are in solution in amounts from 0.005% to 10%, by weight.

3. A pack as recited in claim 2 wherein the said compounds are present in their

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respective components in solution in amounts from 0.05% to 5%, by weight.

4. A pack as recited in any of claims 1—3 wherein the cation is selected from the group consisting of calcium, zinc, iron, indium, rare earth metals, magnesium, manganese, cadmium, aluminium, barium, lanthanum, zirconium, strontium and/or cesium.
5. A pack as recited in any of claims 1—4 wherein the anion is selected from the group consisting of phosphates, C_6 — C_{18} fatty acyl groups, fluoride, fluorophosphate, silico fluoride, molybdate, sulfate, tungstate, β -hydroxyquinolate, tartrate, sorbate, C_6 — C_{18} alkyl sulfonates, carbonates and/or iodates.
6. A pack as recited in claims 4 and 5 wherein the cation is a mixture of calcium and indium cations and the anion is a mixture of phosphate and fluoride anions.
7. A pack as recited in claims 4 and 5 such that the precipitate is selected from the group consisting of $CaMoO_4$; $CaWO_4$; $ZnNH_4PO_4$; $InPO_4$; rare earth phosphates; rare earth fluorides; magnesium alkyl (C_{18}) sulfonate; magnesium stearate; calcium stearate; cadmium iodate; cadmium hydroxide; calcium phosphate; zinc stearate and/or aluminium phosphates.
8. A pack as recited in claim 7 such that the precipitate is selected from the group consisting of lanthanum, cerium and samarium (II) phosphates and lanthanum,

cerium, praseodymium, neodymium and samarium fluorides.

9. A pack as recited in claim 1 wherein the stated components are in the form of two solutions, in which:

- (A) the first solution contains from 0.005% to 10% of a soluble calcium salt, by weight; and
- (B) the second solution contains from 0.005% to 10% of a soluble phosphate salt, by weight.

10. A pack as recited in claim 9 wherein

- (A) the first solution contains from 0.005% to 0.1% of a soluble indium salt, by weight; and
- (B) the second solution contains from 0.005% to 0.1% of a soluble fluoride salt, by weight.

11. A pack as recited in claim 1 substantially as hereinbefore described and exemplified.

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